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SYNTHESIS OF SOME NOVEL MULTI FLUORINATED BARBITURIC ACID DERIVATIVES

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ABSTRACT

*The synthesis of various Barbituric acid derivatives **B1-B12** were carried out by reaction of substituted urea **3a-c** with malonic acid to produced compounds **4a-c** which on treatment with various aldehydes **5a-d** and 2,2-dimethyl-1,3-dioxane-4,6—dione to produced final products **B1-B12***

KEYWORDS: Barbituric acid derivatives, malonic acid, Substituted urea derivatives, ,2-dimethyl-1,3-dioxane-4,6—dione

INTRODUCTION

Barbituric acid is a pyrimidine-2,4,6(1H,3H,5H)-trione. The Chemistry of pyrimidines & its derivatives have been studied for over a century due to their diverse biological activities such as antimicrobial, anticancer, antiHIV, antihypertensive, Cardiac stimulant, antimalerial, antifungal, anticancer, antipyretic, analgesic, anti-inflammatory, potential herbicidal and leishmanicidal[1-17].

One of the most important factors in drug design is that **fluorine** is much more lipophilic than hydrogen; so incorporating fluorine atom in a molecule will make it more fat soluble. This means it percolates into membranes much more readily, and hence the fluorinated molecule has a higher bioavailability. So it is no great surprise that around a fifth of all drugs on the market today contain at least one fluorine substituent.

The inclusion of a **fluorine atom** in a drug molecule can influence not only pharmacokinetic properties, such as absorption, tissue distribution, secretion, and the route and rate of biotransformation but also its pharmacodynamics and toxicology. Introducing **F & CF_3** substituent often improves lipophilicity, and suppresses metabolic detoxification processes to increase the *in vivo* lifetime of drugs.

In a view of the all above facts we have synthesized some novel Barbituric acid derivatives containing Fluorine,Trifluoromethyl and trifluoromethoxy group in its framework.

OBJECTIVES OF PRESENT WORK

1. To synthesize substituted urea derivatives 3a-c by condensation reaction between 4-fluoroaniline and phenylchloroformate to produced phenylcarbamate followed by condensation with various fluorinated anilines.

2. To find out new synthetic pathway for condensation reactions of aromatic aldehydes,meldrum acid and substituted pyrimidines to affords various condensation products B1-B12.

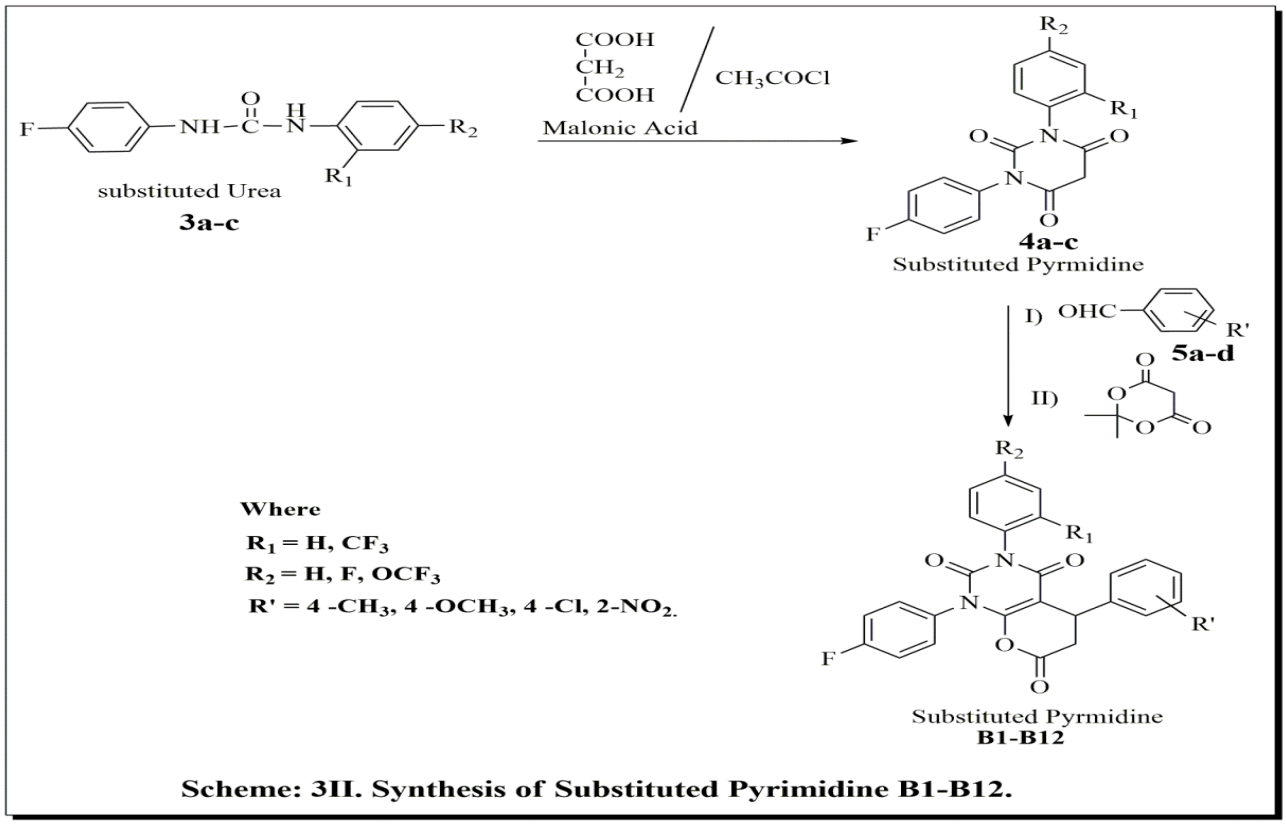
3. To check the scope of the novel protocol for synthesizing a good library of pyrimidine type heterocyclic derivatives.

4. To characterize all the synthesized compounds by ^{1}H NMR, ^{13}C NMR, IR, MASS spectroscopic techniques.

SCHEME

The synthesis of various barbiturates **B1-B12** were carried out by reaction of compounds **3a-c** with malonic acid to produced compounds **4a-c** which on treatment with various aldehydes

5a-d and 2,2-dimethyl-1,3-dioxane-4,6—dione to produced final products **B1-B12** (**Scheme 3II**).



Scheme: 3II. Synthesis of Substituted Pyrimidine B1-B12.

Characteristics data showing the synthesis compounds B1-B12.

From the **Table 3.2** show the various condensation products **B1-B12** of condensation reaction between **various aldehydes and Fluorosubstituted anilines.** It clearly indicates that the compounds bearing electron withdrawing group are synthesized in shorter reaction time as compared to compounds bearing electron donating group. Compounds **B4, B8 & B12** bearing electron withdrawing were synthesized in 6 hr. as shorter time as compared to compound **B1, B5 & B9** bearing electron donating group in 8 hr.

Table 3.2 Characteristic data showing synthesis of compounds B1-B12 from various aldehydes and Fluorosubstituted anilines.

Sr. No.	Compounds Code	R'	R_1	R_2	Reaction Time[a] (min)	% Yiled[b]
1	B1	4-OCH_3	CF_3	H	8	70

2	B2	4-CH_3	CF_3	H	7.5	75
3	B3	4-Cl	CF_3	H	6.5	78
4	B4	2-NO_2	CF_3	H	6.0	85
5	B5	4-OCH_3	CF_3	OCF_3	8	70
6	B6	4-CH_3	CF_3	OCF_3	7.5	75
7	B7	4-Cl	CF_3	OCF_3	6.5	78
8	B8	2-NO_2	CF_3	OCF_3	6.0	85
9	B9	4-OCH_3	CF_3	F	8	70
10	B10	4-CH_3	CF_3	F	7.5	75
11	B11	4-Cl	CF_3	F	6.5	78
12	B12	2-NO_2	CF_3	F	6.0	85

[a]Reaction is monitored by TLC.

[b]Isolated yield

All the compounds were crystallized from hot ethanol and percentage yield was calculated after crystallization step. All the synthesized compounds have been characterized by melting point, ^{1}H NMR, ^{13}C NMR, IR and Mass spectroscopy. All the data were in agreement with the cited literature

EXPERIMENTAL

Melting points were determined using µThermoCal$_{10}$ (Analab scientific Pvt. Ltd.) melting point apparatus and are uncorrected. TLC was carried out using aluminum sheets precoated with silica gel 60 F_{254}.

Chemicals and Reagents

All chemicals used were of laboratory reagent grade and used without further purification**.** Phenylchloroformate (PCF), triethylamine, Acetonitrile, Malonic acid 4-fluoroaniline, various aldehydes, meldrum acid, piperidine were used as received from Merck, Mumbai, India. All the solvent were used as received from Merck, Mumbai, India.

Synthesis

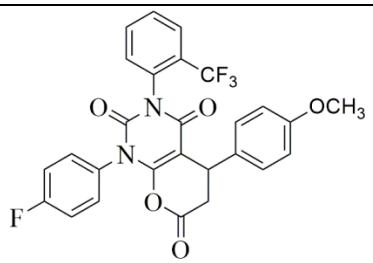
Synthesis of Substituted Urea derivatives 3a-c.

In a 250 ml round bottom flask, **3a-c** (0.01mol) was heated with Malonic acid (0.0115 mol) and acetyl chloride (20 ml) under reflux temperature for 3-4 hr. Cooled mass was then poured into crushed ice under vigorous stirring & stirred for 30 min. The formed precipitates was filtered out, washed & crystallized by MeOH to give **4a-c.** A mixture of **4a-c** (0.01 mol), various aldehydes **5a-d** (0.01 mol), meldrum acid (0.01mol) and catalytic amount of piperidine in 20 ml ethanol was refluxed for **2-3** hr. The reaction mass was cooled to room temperature, separated solid was filtered out and recrystallized by ethanol to give **B1-B12**.

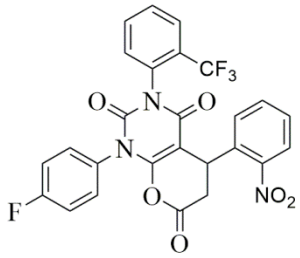
CHARACTERIZATION OF COMPOUNDS B1-B12.

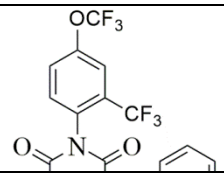
Melting points were determined using µThermoCal$_{10}$ (Analab scientific Pvt. Ltd.) melting point apparatus and are uncorrected. TLC was carried out using aluminum sheets precoated with silica gel 60 F_{254} (Merck). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrophotometer operating at 400 MHz for ^{1}H NMR, and 100 MHz for ^{13}C NMR, as solutions in DMSO-d_6. Chemical shifts (δ) are expressed in ppm and referenced to the residual protic solvent. FT-IR spectra were recorded on Shimadzu FT-IR 8401 spectrophotometer using KBr disc, and are expressed in wave numbers (cm^{-1}). The mass spectra (LCMS) were recorded on Shimadzu LCMS-2010 spectrometer.

Spectral data analysis of selected compounds

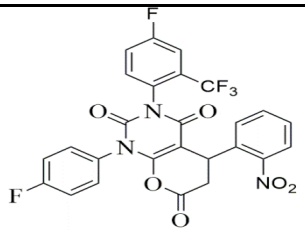
Compound code: B1	
Molecular formula: $C_{27}H_{18}F_4N_2O_5$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, d), 3.6 (3H, s), 4.2 (1H, t), 6.86-7.40 (12H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	36.5, 39.6, 60.1, 128.1, 129.3, 129.8, 131.4, 131.9, 143.6, 151.8,

	153.6, 155.1, 154.8. 159, 163, 170
IR cm^{-1} (KBr):	3050, 1750, 1710, 1644, 1592, 1570, 745.
Mass (M+1):	526.0
Elemental analysis:	**Calculated (%):** C: 61.60; H: 3.45; N:5.32 **Found (%) :** C:61.67; H: 3.76; N:5.86

Compound code: B4	
Molecular formula: $C_{26}H_{15}F_4N_3O_6$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, d), 4.2 (1H, t), 6.86-7.40 (12H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 33.6, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.9, 158, 162, 170
IR cm^{-1} (KBr):	2950, 1750, 1710, 1650, 1614, 1592, 1569, 750.
Mass (M+1):	541.0
Elemental analysis:	**Calculated (%):** C: 57.68; H: 2.79; N: 7.76 **Found (%) :** C: 57.86; H: 2.54; N:7.86

Compound code: B8	
Molecular formula: $C_{27}H_{14}F_7N_3O_7$	

M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, d), 4.2 (1H, t), 6.86-7.40 (11H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 33.6, 39.1, 40.2, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.9, 158, 162, 170
IR cm^{-1} (KBr):	3051, 1750, 1710, 1614, 1592, 1569, 750.
Mass (M+1):	625.0
Elemental analysis:	**Calculated (%):** C: 51.85; H: 2.26; N: 6.72 **Found (%) :** C: 51.89; H: 2.54; N:6.86

Compound code: B12	
Molecular formula: $C_{26}H_{14}F_5N_3O_6$	
M. P. (°C): >250	
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:	3.2 (2H, d), 4.2 (1H, t), 6.86-7.40 (11H, Ar-H, m).
^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:	32.5, 33.6, 39.1, 128.1, 129.3, 130.1, 131.4, 131.9, 143.6, 151.8, 153.6, 155.1, 155.9, 158, 162, 170
IR cm^{-1} (KBr):	3051, 1750, 1710, 1614, 1592, 1569, 750.
Mass (M+1):	559.0
Elemental analysis:	**Calculated (%):** C: 55.82; H: 2.52; N: 7.51 **Found (%) :** C: 55.89; H: 2.54; N:7.86

CONCLUSION

In tallness, we include synthesized of novel fluorinated Barbituric acid derivatives using easy and proper method. This method produces these products in supreme yields and difficulty-free workup.

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